



## Case report

## A rare cause of cystic lung disease – Birt-Hogg-Dubé syndrome



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## ABSTRACT

Birt-Hogg-Dubé syndrome, initially described in 1977, is an autosomal dominant inherited condition characterised by basal pulmonary cysts often resulting in pneumothorax, renal tumours and cutaneous involvement. Lung cysts have been described in up to 90% of patients with a corresponding risk of pneumothorax of 50 times greater than the normal population. We describe here a case of Birt-Hogg-Dubé diagnosed in the 9th decade of life and discuss the radiological findings and clinical implications.

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## 1. Introduction

Birt-Hogg-Dubé syndrome, initially described in 1977 [1], is an autosomal dominant inherited condition characterised by basal pulmonary cysts often resulting in pneumothorax, renal tumours and cutaneous involvement. Lung cysts have been described in up to 90% of patients with a corresponding risk of pneumothorax of 50 times greater than the normal population [2]. We describe here a case of Birt-Hogg-Dubé diagnosed in the 9th decade of life and discuss the radiological findings and clinical implications.

## 2. Case report

An 82-year-old man was referred to the chest clinic with recurrent chest infections, and insidious onset of shortness of breath and episodic cough over several years. Past medical history was significant for CABG in 1996, following 2 myocardial infarctions and ex-tobacco use accruing approximately 80 pack years. Family history was remarkable in that his brother and 2 out of 3 daughters have had spontaneous pneumothoraces all presenting in the 3rd to 4th decade of life. Examination revealed diminished breath sounds

on auscultation and a few crackles at his right base. Multiple whitish dome shaped papules located mainly on the head and neck in keeping with fibrofolliculoma were noted (Fig. 1). Spirometry demonstrated mild obstruction with preserved lung volume. A chest radiograph was reported as normal. A HRCT scan was requested and characteristic features were noted (Fig. 2a+b). A skin biopsy was performed, although suggestive was non-diagnostic. The patient was referred for genetic testing which revealed a mutation in the exon of the FLCN gene located on chromosome 17, confirming the diagnosis (Table 1).

## 2.1. CT findings

In this case, given the patients illustrious smoking history, it is important to make the distinction that the air-containing lesions are classified as cysts instead of bullae. A lung cyst is defined radiologically by the Fleischner Society as a “round parenchymal lucency or low attenuating area, which is usually thin walled and contains air, but occasionally fluid or solid material” [3]. In comparison bullae are usually accompanied by emphysematous changes in the adjacent lung typically involving the peripheral regions of the upper lobes.

The major differential of cystic lung disease include Lymphangioleiomyomatosis (LAM), sporadic or associated with tuberous sclerosis, Langerhans Cell Histiocytosis (LCH), Lymphocytic Interstitial Pneumonia (LIP) and the Folliculin (FLCN) syndrome also known as Birt-Hogg-Dubé (BHD). PCP related pneumocystis is also a consideration however in this case the clinical history would

Abbreviations: BHD, Birt-Hogg-Dubé syndrome; FLCN, folliculin; HRCT, high resolution computed tomography; LAM, lymphangioleiomyomatosis; LCH, langerhans cell histiocytosis; LIP, lymphocytic interstitial pneumonia; mTOR, mammalian target of rapamycin; PCP, jirovecii pneumonia.

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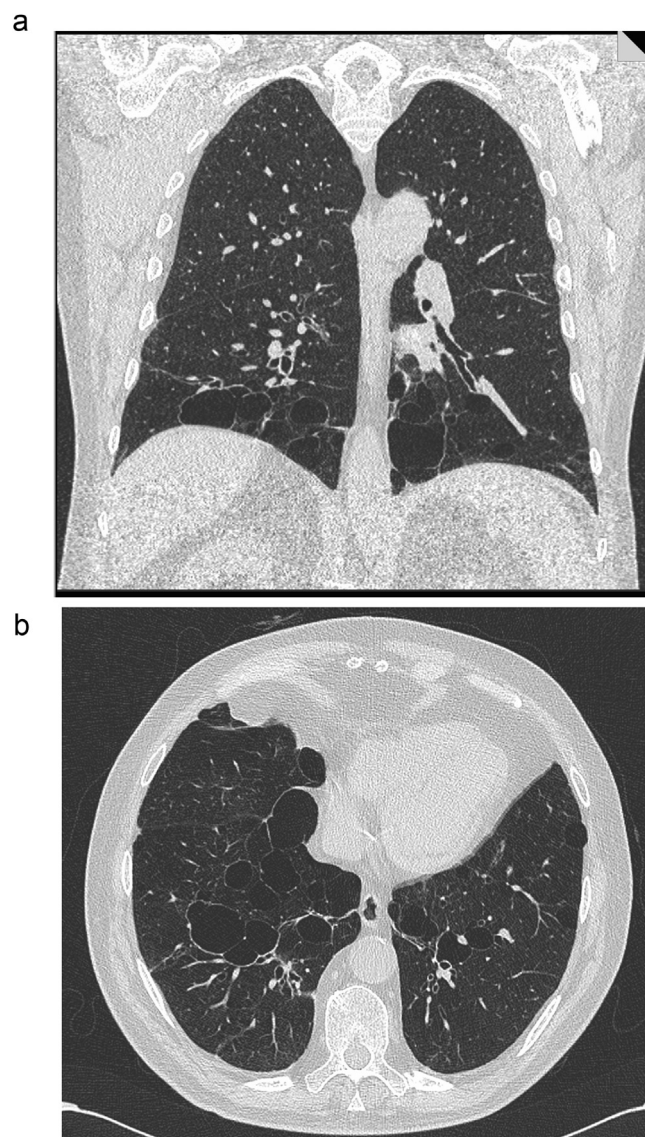
**Fig. 1.** Fibrofolliculomas.

generally exclude this entity.[4] There is often overlap in imaging appearances; distinguishing features including the size and distribution of pulmonary cysts, associated lung parenchymal involvement and clinical features aid differentiation [5].

The cysts are typically small and round in LAM with uniform lung distribution, increased lung volumes and septal thickening may also be present [6]. Sporadic LAM presents almost exclusively in females of childbearing age, up to one third of cases are associated with the Tuberous Sclerosis Complex. The cysts and nodules in LCH, predominantly seen in young male smokers are typically distributed in the upper lobes with relative sparing of the costophrenic recesses, tips of the lingula and middle lobe [7]. Radiological findings in LIP consist of small thin-walled cystic airspaces seen in a random distribution in approximately two-thirds of patients, usually associated patchy areas of ground glass attenuation, as well as diffuse poorly defined nodules and septal thickening.[8] This condition is most commonly seen in association with acquired immunodeficiency syndrome (AIDS) and Sjögren's syndrome. Cysts in BHD are typically basilar, can be peripheral or central and vary in size (1–5 cm or even larger) and shape. In this case multiple thin-walled round, elliptical or lentiform well-defined clear cysts (1–5 cm), in a predominant basilar and medial subpleural distribution with no other significant additional pulmonary involvement was observed in keeping with the radiological diagnosis [9].

### 3. Discussion

Lung cysts have been described in up to 90% of patients with a corresponding risk of pneumothorax of 50 times greater than the normal population [2, 9]. The right lung is more frequently affected although both lungs are affected in up to one quarter of cases [10]. The literature describes a high degree of clinical variability, and therefore the condition is often undiagnosed. Up to 70% of patients with Birt-Hogg-Dubé syndrome presenting with pneumothorax do not have a prior diagnosis of renal or cutaneous disease [2]. Among the previously published case reports, the youngest case of BHD syndrome with spontaneous pneumothorax was 7 years of age [11]. The mean age of presentation is 38 years with up to one quarter presenting with a pneumothorax, there is no clear predilection for



**Fig. 2.** Representative Coronal (a) and Axial (b) CT Thorax Images revealing multiple thin-walled round, elliptical or lentiform well defined clear cysts (1–5 cm), in a predominant basilar and medial subpleural distribution, with preserved lung volumes and no other significant additional pulmonary involvement.

either sex. To the best of our knowledge our patient represents the oldest index case reported in the literature thus far.

In 2002, the FLCN gene was identified as being associated with Birt Hogg Dubé syndrome [12]. This gene, located on chromosome 17p11.2 encodes the protein folliculin, which is expressed in most tissues including skin, type 1 pneumocytes and the distal nephron [13]. Although the function of folliculin is unknown, there is increasing evidence that the FLCN gene plays a role in tumor suppression-it has been found to mediate cellular activities by interacting with the mammalian target of rapamycin (mTOR) [14].

The risk of developing renal tumors is high in BHD and therefore management is focused on early diagnosis and treatment of renal tumours. The prevalence of renal tumors associated with mutations in the FLCN gene varies from 6.5% to 34% according to different studies [15]. The average age at renal tumor detection has been reported as 50.4 years and multiple tumors are found in the majority of patients [16]. Current opinion suggests MRI imaging and

**Table 1**

Criteria proposed by the European Birt-Hogg-Dubé Consortium.

Major criteria
At Least 5 fibrofolliculomas or trichodiscomas, at least 1 confirmed histologically, of adult onset
Pathogenic germline mutation in FLCN
Minor criteria
Multiple lung cysts: basally located with no other apparent cause, with or without spontaneous pneumothorax
Renal cancer: early onset (<50 years), multifocal or bilateral renal cancer, or renal cancer of characteristic forms (oncocytic-chromophobe hybrid histology)
First-degree relative with Birt-Hogg-Dubé syndrome

Patients should fulfil 1 major or 2 minor criteria for diagnosis.

regular follow up are required from the age of 20. A large range of benign and malignant tumors has been described in patients with BHD however a causal relationship has not been proven. In 1975, Hornstein et al. described the combination of skin fibrofolliculomas and colorectal polyps [17]. This condition is now considered to be identical to BHD, but whether BHD is associated with an increased risk of colorectal neoplasia is uncertain [18]. An increased risk of colorectal cancer might apply only to specific patient subgroups therefore periodic colonoscopy might be considered in families with BHD.

#### 4. Conclusion

The literature describes a high degree of clinical variability in this rare condition therefore it is often undiagnosed [2]. Birt-Hogg-Dubé syndrome should be suspected in patients with basally located lung cysts with no other apparent cause. Management is focused on early diagnosis and treatment of renal tumours.

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